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Partners in crime: TNFα-based networks promoting cancer progression.

Adit Ben-Baruch

The Shmunis School of Biomedicine and Cancer Research, George S. Wise Faculty of Life Sciences, Tel Aviv University, Israel

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***Correspondence:** Adit Ben-Baruch. The Shmunis School of Biomedicine and Cancer Research, George S. Wise Faculty of Life Sciences, Tel Aviv University, Israel. E-mail: aditbb@tauex.tau.ac.il
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Abstract

Tumor necrosis factor α (TNFα) has been characterized as a potent pro-inflammatory cytokine, being responsible for the anti-tumor effects of Coley's toxins, reported at the beginning of the 20th century. However, extensive research of TNFα indicated that continuous presence of TNFα in tumors contributes to chronic tumor inflammation, and that the cytokine is a potent tumor-promoting and metastasis-enhancing factor.

Along these lines, we have demonstrated the ability of TNFα to induce a large variety of pro-metastatic functions in breast tumor cells and in stromal cells, acting in cooperativity with other tumor-supporting factors of the tumor microenvironment and with intracellular oncogenes. The signaling pathways mediating these collaborative activities of TNFα with other cancer-promoting elements have been identified in our studies, revealing a rich array of molecular setups acting under different stimulatory conditions.

Our current studies focus on the roles and regulation of TNFα receptors, TNFR1 but mainly TNFR2, in breast cancer progression. Reports that analyzed all breast cancer subtypes as a whole demonstrated metastasis-supporting roles for TNFR2 in breast cancer; in contrast, our research has addressed specifically the most aggressive triple-negative subtype of breast cancer (TNBC) and found that high TNFR2 expression by tumor-infiltrating lymphocytes (TILs) and by TNBC cells in patient tumors was significantly connected to improved patient prognosis.

Following up on these findings, we demonstrated that in chemotherapy-treated TNBC tumors the CD8+ TNFR2+ TIL population was associated with reduced tumor growth in syngeneic mice. Our recent observations suggest that these CD8+ TNFR2+ TILs carry cytotoxic functions, and that chemotherapy leads to selection or preferred proliferation of CD8+ TNFR2+ TILs that have the ability to eradicate cancer cells.

Moreover, our ongoing studies provide evidence to strong tumor-promoting activities of TNFR1 in TNBC cells, while TNFR2 has opposing and protective roles. We identified regulatory functions for WT TNFR2 and for a SNP-TNFR2 variant (depending on the conditions), leading to reduced tumor cell spontaneous and directed migration, lower release of pro-inflammatory chemokines and ICAM-1 expression, and down-regulation of pro-inflammatory signaling.

The observations of our recent studies suggest that in TNBC tumors TNFR2 has metastasis-inhibitory functions and thus it may not be a suitable therapeutic target in TNBC. Rather, we propose that TNBC patients should be treated by TNFR1-specific modalities, while sparing TNFR2; under such conditions, CD8+ TNFR2+ TILs may acquire more efficient anti-tumor activities in the presence of inhibitory immune checkpoints, and the metastatic potential of TNFR2+ tumor cells may be reduced.